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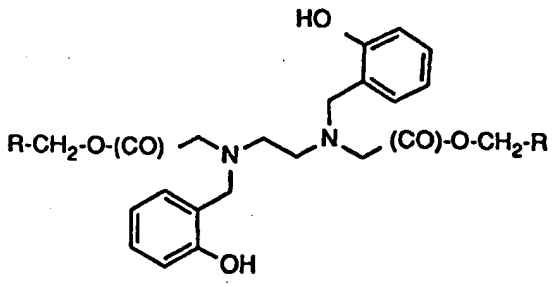
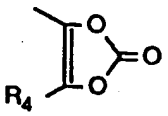
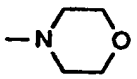


(I)



(a)



(b)

(57) Abstract

[N,N'-bis(2-hydroxybenzyl)ethylenediamine N,N'-diacetic acid] derivatives of formula (I) in which R represents -(CO)-R_1, -O-(CO)-R_2, -O-(CO)-O-R_3 or (a) wherein R_1 is -NR_4R_5 or (b); whereby R_4 and R_5 are independent of each other C_1-C_3 alkyl or C_3-C_7 cycloalkyl or form together the group -$(CH_2)_n$-, n is an integer from 3 to 6; R_2 is C_1-C_6 alkyl, unsubstituted phenyl or phenyl substituted by one to four substituents selected from the group consisting of halogen and hydroxy; R_3 is C_1-C_6 alkyl or C_3-C_7 cycloalkyl; R_4 is C_1-C_3 alkyl; and salts thereof form chelate-type metal complexes with trivalent metal ions, especially iron (III), and can be used, for example, for the treatment of pathological conditions in warm-blooded animals that are associated with an excess of trivalent metal ions in the body.

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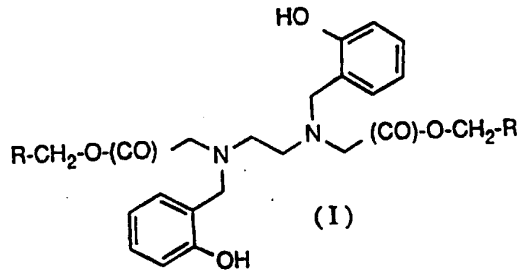
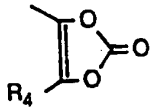
N,N'-BIS (2-HYDROXYBENZYL) ETHYLENEDIAMINE-N,N'-DIACETIC ACID DERIVATIVES AS CHELATING AGENTS

The invention relates to novel and systemically effective chelating agents embracing the derivatives of [N,N'-bis(2-hydroxybenzyl)ethylene diamine N,N'-diacetic acid] of the formula (I) as shown below, processes for their manufacture, pharmaceutical compositions containing such compounds, and the use of these derivatives. The invention is also directed to alkali and alkaline earth metal salts of [N,N'-bis(2-hydroxybenzyl)ethylene diamine N,N'-diacetic acid] derivatives which represent valuable starting material and exhibit valuable therapeutical properties.

The invention relates especially to [N,N'-bis(2-hydroxybenzyl)ethylene diamine N,N'-diacetic acid] derivatives of the formula (I)



(I)

in which R represents -(CO)-R_1, -O-(CO)-R_2, -O-(CO)-O-R_3 or  wherein

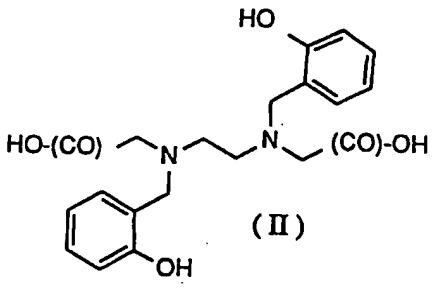
R_1 is -NR_4R_5 or  ; whereby R_4 and R_5 are independent of each other C_1-C_3 alkyl or C_3-C_7 cycloalkyl or form together the group -$(CH_2)_n$-, n is an integer from 3 to 6;

R_2 is C_1-C_6 alkyl, unsubstituted phenyl or phenyl substituted by one to four substituents selected from the group consisting of halogen and hydroxy;

R_3 is C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

R_4 is C_1-C_3 alkyl; and salts thereof, processes for the manufacture of these compounds, pharmaceutical compositions containing such compounds and the use of these compounds.

The compounds of the formula (I) represent derivatives of HBED which is [N,N'-bis-(2-hydroxylbenzyl)ethylene diamine N,N diacetic acid] a product of the formula (II)



(II)

HBED is described as a chelating agent for the treatment of iron overload in U.S. patent US-4'528'196. As tests in monkeys and human beings show, the major advantage of the compounds of the formula (I) over HBED is that the free molecules do not bind to heavy metal ions at all. Thus, they pass the intestinal tract without any loss. As free molecules they do not take up heavy metal ions but develop this metal binding properties surprisingly after their resorption when they circulate in the blood stream so that they can successfully be administered systemically to warm-blooded animals, most preferred orally or parenterally. Administered orally they even exhibit a significantly higher activity than HBED. Thus the present invention provide agents that are even effective chelators when administered systemically. Although the free molecules of the formula (I) do not bind to heavy metal ions they develop strong chelating properties in the animal's blood.

A therapeutically preferred subgroup within the formula (I) consists of those representatives wherein R is defined as under Formula (I) and
R_1 is $-NR_4R_5$ whereby R_4 and R_5 are independent of each other C_1-C_3 alkyl;
R_2 is C_1-C_3 alkyl;
R_3 is C_1-C_3 alkyl or C_3-C_7 cycloalkyl;
halogen is fluorine, chlorine or bromine;
cycloalkyl is cyclohexyl;
R_4 is methyl; and salts thereof.

Most preferred are however compounds of the formula (I) wherein R represents $-O-(CO)-R_2$ and R_2 C_1-C_6 alkyl and preferably C_1-C_3 alkyl.

Within the scope of the present description, the definitions used hereinbefore and hereinafter have preferably the following meanings: C_1-C_6 alkyl stands for an unbranched or branched alkyl group characterized by the given number of carbon atoms. Typical representatives are methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, tert-pentyl, neo-pentyl, n-hexyl, 1-methyl-pentyl, 1,1-dimethyl-butyl, 3,3-dimethyl-butyl, 2,2-dimethyl-butyl, 2-methyl-pentyl, 3-methyl-pentyl, and 4-methyl-pentyl. Halogen is, for example, fluorine, bromine or chlorine, preferably fluorine or chlorine. C_3-C_7 cycloalkyl represents a carbocyclic saturated ring with three to seven carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopentyl or cyclohexyl.

Most preferred representatives within the scope of formula (I) are the following ones:
Bis N,N-diethylaminocarbonylmethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis acetoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis n-propoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis iso-propoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N N'-diacetate;
Bis acetoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis tert-butoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis n-pentoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis phenoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis ethoxycarbonyloxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis cyclohexyloxycarbonyloxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis (4-methyl-1,3-dioxolan-2-on-4-yl)methoxy-[N,N'-bis(2-hydroxybenzyl)]-ethylenediamine N,N'-diacetate; and
Bis N-morpholinocarbamoylmethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate.

The compounds of the formula (I) are capable of forming salts. The salts of the compounds according to the invention are, especially, pharmaceutically acceptable, non-toxic salts. Such salts are especially metal salts and ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts as well as related 2+ salts such as zinc salts, and ammonium salts with ammonia or suitable organic amines, there coming into consideration for the salt formation especially

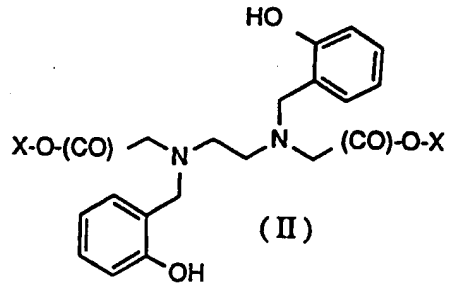
aliphatic, cycloaliphatic, cycloaliphatic-aliphatic or araliphatic primary, secondary or tertiary mono-, di- or poly-amines, and also heterocyclic bases. Such amines are, for example, lower alkylamines, for example triethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tris-(2-hydroxyethyl)-amine, basic aliphatic esters of carboxylic acids, for example 4-aminobenzoic acid 2-diethylaminoethyl ester, lower alkyleneamines, for example 1-ethylpiperidine, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N'-dibenzyl-ethylenediamine, also bases of the pyridine type, for example pyridine, collidine or quinoline. The compounds of the formula (I) can also form intermolecular (as opposed to intramolecular, i.e. zwitterionic) acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulphuric acid or phosphoric acid, or with suitable organic carboxylic or sulphonic acids, for example methanesulfonic acid, or with amino acids, such as arginine and lysine.

For isolation and purification, pharmaceutically unacceptable salts also can be used. Only the pharmaceutically acceptable, non-toxic salts are used for therapeutic application and, for that reason, they are preferred.

Taken up by the a warm-blooded animal, the compounds of the formula I are transformed into a form that allows them to form stable complexes with metal ions, especially heavy metal ions. Of the heavy metal ions, there may be mentioned especially those in the 3+ oxidation state, such as Al^{3+} or, most especially, Fe^{3+}.

Thus, the substances of the formula (I) exhibit valuable pharmacologically properties when administered systemically, especially after oral or percutaneous application. Owing to their ability to form in the animal's body stable complexes with heavy metal ions, especially with those in the 3+ oxidation state, such as Al^{3+} or, most especially, with Fe^{3+}, the compounds of the formula (I) prevent, for example, the deposition of iron-containing pigments in the tissues and, in cases where iron has been deposited in the organism, bring about elimination of the iron, for example in haemochromatosis and haemosiderosis and also in cirrhosis of the liver. They can also be used for the elimination from the organism of other heavy metals, for example aluminium and also chromium and copper. Thus, the compounds of the formula I can also be used in the case of dialysis encephalopathy, osteomalacia and Alzheimer's disease.

The compounds of the formula (I) according to the invention and salts thereof can be manufactured by chemical synthesis according to processes known per se. They are manufactured, for example, by adding under cooling sodium hydride or potassium hydrogene carbonate to the compound of the formula (II)



(II)

wherin X stands for hydrogen or the group $-CH_2J$ and adding to the resultant solution either

(a) in those cases where X stands for hydrogen a compound of the formula (III)

$$Y\text{-}CH_2\text{-}R \quad \text{(III)}, \text{ or}$$

(b) in those cases where X stands for the group $-CH_2J$ a compound of the formula (IV)

$$HO\text{-}C(O)\text{-}R \quad \text{(IV)},$$

whereby R in the formulae (III) and (IV) is defined as under formula (I) and Y represents halogen, preferably chlorine, bromine or iodine, most preferably bromine or iodine.

The compound of the formula (II) wherin X is hydrogen is HBED which is as mentiond above described in the U.S. patent US-4'528'196. The compound of the formula (II) wherin X is $-CH_2J$ can be prepared by reacting HBED with CH_2ClJ under suitable conditions. This type of reaction is described in the literature and well known to the skilled chemist.

The reaction is performed in a inert dipolar aprotic solvent such as acetone, acetonitrile, nitromethane, dimethylformamide (DMF), dimethylacetamide (DMA), tetrametylurea, dimethylsulfoxide (DMSO), tetrahydrothiophen-1,1-dioxide (sulfolane) or diether of ethylenglycole at relatively low temperatures preferably at temperatures arround 0°C, for

example at about -10° to 30°C, and preferably under an inert gas atmosphere.

Salts of compounds of the formula (I) can be manufactured in a manner known per se. Thus, acid addition salts of compounds of the formula (I) are obtained in customary manner, for example by treating with an acid or a suitable anion-exchange reagent. Internal salts of compounds of the formula (I) (zwitterionic forms) can be formed, for example, by neutralising the compounds or salts, such as acid addtion salts, to the isoelectric point, for example with weak bases, or by treating with liquid ion-exchangers.

Salts can be converted in customary manner into the free compounds: metal and ammonium salts can be converted into the free compounds, for example, by treating with suitable acids, and acid addition salts, for example, by treating with a suitable basic agent.

The starting materials, especially those of formula (II) and (III) are available commercially and/or known or can be manufactured by known processes.

The pharmacologically acceptable compounds of the present invention can be used, for example, for the manufacture of pharmaceutical compositions which contain an effective amount of the active substance together or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers.

The pharmaceutical compositions according to the invention are those which are suitable for enteral, such as oral, administration and for parenteral, such as subcutaneous, administration to warm-blooded animals, especially humans, and which contain the pharmacological active substance on its own or together with a pharmaceutically acceptable carrier. The dosage of the active substance depends on the species of warm-blooded animal and on the age and individual condition, the illness to be treated and also on the mode of administration.

The novel pharmaceutical proparations contain from approximately 10 % to approximately 95 %, preferably from approximately 20 % to approximately 90 %, of the active substance. Pharmaceutical compositions according to the invention can, for example, be in unit dose form, such as dragées, tablets, capsules, suppositories or ampoules, and contain from approximately 0.1 g to approximately 3.0 g, preferably from approximately 0.3 g to approximately 1.0 g, of the active ingredient.

The pharmaceutical compositions of the present invention are manufactured in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. Pharmaceutical compositions for oral use can be obtained by combining the active substance with one or more solid carriers, if desired granulating a resulting mixture and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, to form tablets or dragée cores. In so doing, they can also be incorporated into plastics carriers which release the active substances or allow them to diffuse in controlled amounts.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders such as starches, for example corn, wheat, rice or potato starch, gelatine, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinyl-pyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow-regulating and lubricating agents, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings that are, if desired, resistant to gastric juice, there being used, inter alia, concentrated sugar solutions which optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures or, for the manufacture of coatings that are resistant to gastric juice, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropyl-methylcellulose phthalate. Colouring substances or pigments can be added to the tablets or dragée coatings, for example for the purpose of identification or for indicating different doses of active substance.

Other orally administrable pharmaceutical compositions are dry-filled capsules made of gelatin, and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquids or wax-like substances, such as fatty oils, paraffin oil or polyethylene glycols, it being possible also for stabilisers to be added.

Other forms of oral administration are, for example, syrups prepared in customary manner that contain the active ingredient in, for example, suspended form and in a concentration of approximately from 5 % to 20 %, preferably approximately 10 %, or in a similar concentration that provides a suitable single dose when administered, for example, in measures of 5 or 10 ml. Also suitable are, for example, powdered or liquid concentrates for preparing shakes, for example in milk. Such concentrates can also be packed in single-dose quantities.

Particularly suitable dosage forms for parenteral administration are sterile aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, or sterile aqueous injection suspensions which contain substances increasing the viscosity, for example sodium carboxymethyl cellulose, sorbitol and/or dextran, and optionally stabilisers. In addition, the active ingredient, with or without adjuvants, can also be in lyophilised form and brought into solution prior to parenteral administration by addition of suitable solvents.

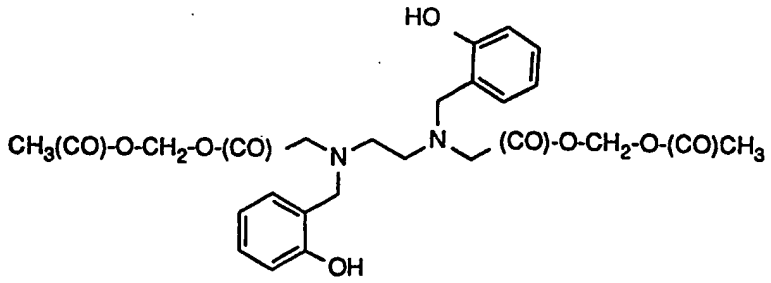
The invention relates also to compositions for diagnostic purposes that contain a suitable metal complex of a compound of the formula (I), preferably in the form of an aqueous solution or in the form of a dry preparation.

The invention relates also to a method of treatment of pathological conditions in a mammal, especially human, which, as has been described hereinbefore, are associated with an excess of a trivalent metal cation such as aluminium or, especially, iron(III), in the body, which method comprises administering, preferably orally, a prophylactically or therapeutically effective amount of a compound of formula (I) or of a pharmaceutically acceptable salt thereof. There are used for this purpose especially the above-mentioned pharmaceutical compositions, a daily dose of from approximately 25 mg/kg to approximately 200 mg/kg, preferably from approximately 20 mg/kg to approximately 150 mg/kg, of a compound of the present invention being administered to a warm-blooded animal. The dosage can be administered orally in several, for example three, individual doses. For systemic, e.g. subcutaneous, administration the more water soluble salt forms of the compounds of the formula (I), e.g. the sodium salt, are preferred. Most preferred mode of administration is orally. An alternatively mode of administration is subcutaneously.

The invention concerns especially the compounds of the formula (I), the methods for their preparation as outlined above, pharmaceutical compositions containing as active ingredient a compound of the formula (I). Preferred are pharmacetical compositions for systemic administration, as described generally and in the examples, and especially the oral dosage forms. The invention further concerns a method of treatment of pathological conditions in a mammal that are associated with an excess of trivalent metal ions in the body, comprising administering systemically, most preferred orally, to said mammal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The following examples serve to illustrate the invention but should not be construed as a limitation thereof. Temperatures are given in degrees Centigrade.

Example 1: Bis acetoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine-N,N'-diacetate



HBED (1g, 2.57 mMol) was dissolved in 15 ml of dimethylformamide, the resulting solution cooled to 0-4 C and kept under innert atmosphere. Sodium hydride (280 mg, 6.43 mMol, 55-60% suspension in oil) was added and the resulting suspension stirred 30 min. at 0-4 C.

Bromomethylacetate (656 ml, 6.7 mMol) was added and the reaction mixture stirred for 5 h at room temperature.The mixture was poured in ethylacetate (100 ml) and washed with water (3 X 50 ml), brine (1X50ml) dried with Na_2SO_4, after filtration of the drying agent the solvent was evaporated under reduced pressure.

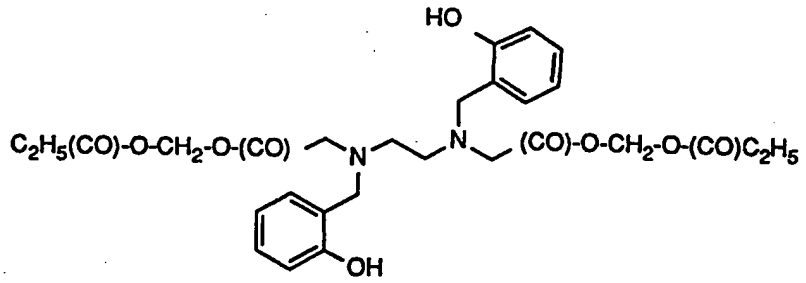
The residue was purified on a chromatographic column containing 70g of silicagel and ethylacetate/hexane 1:1 v/v as eluting solvent. The fractions containing the pure

compound were combined and concentrared in vacuo. The residue is recristallized from ethylacetate/hexane to yield the desired compound as a white crystals, mp 100-101°C.

% calc. for $C_{26}H_{32}N_2O_{10}$:	C 58.64
	H 6.06
	N 5.26
	O 30.04
% found :	C 58.52
	H 6.12
	N 5.18
	O 29.91

^{1}H-NMR ($CDCl_3$, 200 MHz) : 2.13 (s, 6H, 2 X H_3CO-); 2.75 (s, 4H, N-CH_2-CH_2-N); 3.12 (s, 4H, 2 X N-CH_2-CO-); 3.78 (s, 4H, 2 X -N-CH_2-PH); 5.79 (s, 4H, 2 X O-CH_2-O); 6.7-7.22 (m, 8H, 2 X Ph).

Example 2 : Bis propanoyloxymethyl [N,N'-bis(2-hydroxybenzyl)]ethylene-diamine N,N'-diacetate



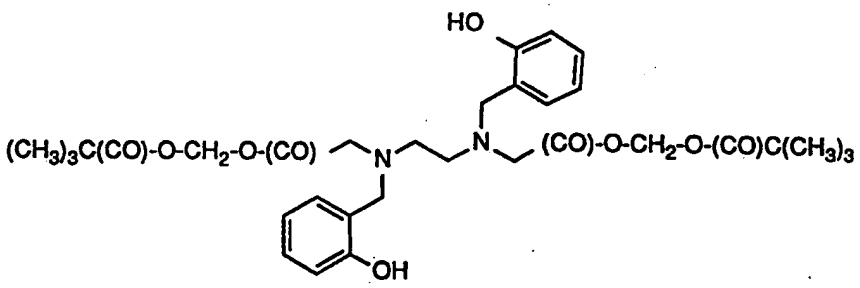
HBED (5.7g, 14.6 mMol) was dissolved in 100 ml DMF (N, N-dimethylformamide) and $KHCO_3$ (5.9g, 58.7 mMol) was added. The mixture was stirred for 50 min.

After that period bromomethylpropionate (6.9ml, 61.67 mMol) was added and the mixture stirred for 18 h.

The reaction mixture was then poured in ethylacetate (100ml) and washed with water (2X200ml), brine (1X200ml) and dried over Na_2SO_4. After filtration the solution was concentrated in vacuo. The residue was recrystallized from ethylacetate/hexane yielding the desired compound with a melting point of 91-92 C.

% calc. for $C_{28}H_{36}N_2O_{10}$:	C 59.99
	H 6.47
	N 5.0
	O 28.54
% found :	C 60.1
	H 6.6
	N 5.0
	O 28.2

Example 3 : Bis pivaloyloxymethyl [,N'-bis(2-hydroxybenzyl)]-ethylendiamine N,N'-diacetate



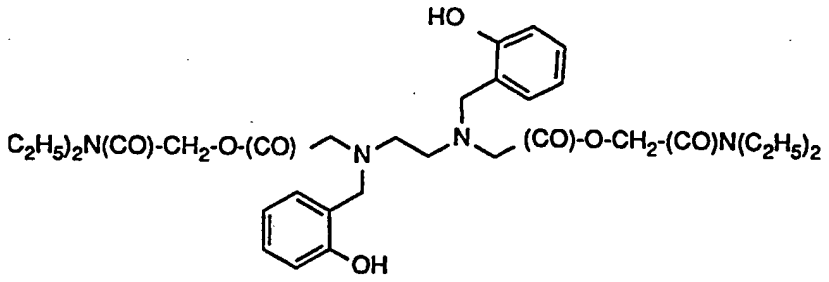
HBED (100mg, 0.255 mMol) was dissolved in 5 ml of DMF, cooled at 0-4 C and kept under Ar. Sodium hydride (23mg, 0.52 mMol, 55-60% in oil) was added and the resulting mixture stirred for 18 h at 6-8 C.

After that time the reaction was diluted with ethylacetate (30ml) and washed with water (2X10ml), brine (1X10ml) and dried over Na_2SO_4. After filtration f the drying agent the solvent was evaporated in vacuo.

The residue was purified on a chromatographic column and the fractions containing the pure compound were combined and evaporated in vacuo to give the desired product as a colorless oil.

^{1}H-NMR ($CDCl_3$, 200 MHz) : 1.2 (s, 9H, -$(CH_3)_3$); 2.75 (s, 4H, N-CH_2-CH_2-N); 3.32 (s, 4H, 2 X N-CH_2-CO); 3.77 (s, 4H, N-CH_2-Ph); 5.8(s, 4H, 2 X -CH_2-Ph); 6.7-7.25(m, 8H, 2 X-Ph).

Example 4: Bis N,N-diethylaminocarbonylmethyl-[N,N'-bis(2-hydroxybenzyl)]-ethylenediamine N,N'-diacetate

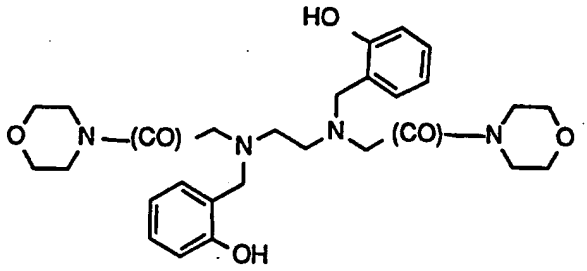


HBED (200mg, 0.51 mMol) was dissolved in anhydrous DMF and cooled to 0-4 C under Ar. Sodium hydride (52mg, 1.2 mMol, 55-60 % in oil) was added and the resulting suspension was stirred for 30 min. Then 2-chloro-N,N-diethylacetamide (168ml, 1.23 mMol) and sodium iodide (18mg, 0.12 mMol) were added and the resulting suspension stirred for 24 h at room temperature.

After that period the reaction mixture was diluted with ethylacetate (50ml) and washed with sat. NH_4Cl (2X20ml), water (1X25ml), brine (1X20ml), dried with Na_2SO_4 and filtrated. The solvent was evaporated in vacuo and the reidue purified on a chromatographic column. The fractions containing the pure compound were combined and concentrated in vacuo to give the desired compound as a colorless oil.

^{1}H-NMR ($CDCl_3$, 200 MHz) : 1-1.2 (m, 12H, 4X -CH_3); 2.8 (s, 4H, N-CH_2-CH_2-N); 3.2 (q, 4H, 2X -CH_2-CH_3); 3.3 (q, 4H, 2X -CH_2-CH_3); 3.45 s, 4H, N-CH_2-CO); 3.8 (s, 4H, N-CH_2-Ph); 4.75 (s, 4H, -O-CH_2-CO); 6.65-7.2 (m, 8H, 2X -Ph).

Example 5: Bis-N-morpholinocarbonylmethyl-[N,N'-bis(2-hydroxybenzyl)]-ethylene-diamine N,N'-diacetate

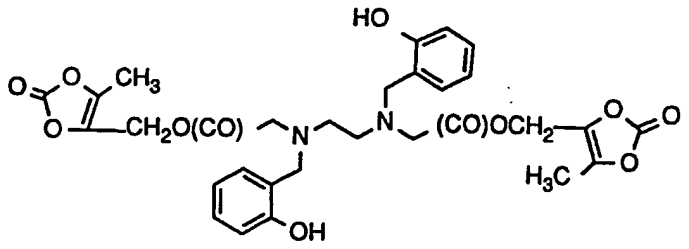


HBED (200 mg, 0.51 mmol) was dissolved in anhydrous DMF (5ml) and cooled to 0-4 °C. NaH (50 mg, 1.12 mmol) was added and the suspension stirred for one hour. Then 2-bromo N-morpholinoacetamide was added and the reaction stirred for seven hours at room temperature.

After that period the reaction mixture was diluted with ethylacetate (30ml) washed with water (2 X 10 ml), brine (1 X 10 ml) dried over Na_2SO_4. After filtration of the drying agent, the solvent was evaporated and the residue chromatographed on column. The fractions containing the pure compound were combined and the solvent evaporated in vacuo to yield the desired product as an oil.

^{1}H-NMR ($CDCl_3$, 200 MHz) : 2.81 (s, 4H, N-CH_2-CH_2-N); 3.42 (s, 4H, N-CH_2-CO); 3.3-3.7 (m, 16H, 2 X N-CH_2-CH_2-O); 3.78 (s, 4H, 2 X N-CH_2-Ph); 4.76 (s, 4H, 2 X O-CH_2-CO); 6.7-7.2 (m, 8H, 2 X -Ph).

Example 6: Bis(5-methyl-1,3-dioxolan-2-one-4-yl)methoxy-[N,N'-bis(2-hydroxybenzyl)]-ethylenediamine-N,N'-diacetate.



HBED·$4H_2O$ (1.31 g, 2.84 mmol) was dissolved in 40ml DMF (dimethylformamide). $KHCO_3$ (potassium bicarbonate) (0.85 g, 8.5 mmol) was added and the reaction mixture was warmed to 65 °C for one hour. The solution was then cooled to 15 °C and 4-bromomethyl--5-methyl-1,3-dioxolan-2-on 1.92 g, 9.94 mmol) in 10 ml DMF was added and the resulting solution stirred for two and a half hours at room temperature.

After that period the solution was diluted in 150 ml of ethylacetate and washed with water (4 X 80 ml). The water phases were extracted with ethylacetate (100 ml). The organic phases were combined, dried with Na_2SO_4 and evaporated in vacuo. The residue was purified on a chromatographic column and the fractions containing the pure compound were evaporated in vacuo. The residue was recrystallized from ethylacetate/hexane to yield the desired compound with a melting point of 111-113 °C.

% calc. for $C_{30}H_{32}N_2O_{12}$:	C 58.82
	H 5.27
	N 4.57
	O 31.34
% found :	C 58.7
	H 5.2
	N 4.6
	O 31.4

Example 7: Pharmaceutical composition for oral administration

1000 gelatine capsules each containing 150 mg of active ingredient are manufactured as follows:

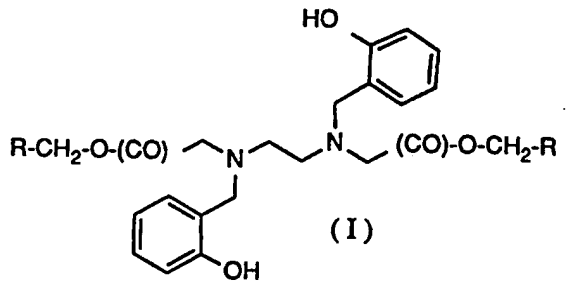
Composition:

150 g Bis acetoxymethyl-[N,N'-bis(2-hydroxybenzyl)]-ethylenediamine N,N'-diacetate
36 g talc
24 g wheat starch
16 g magnesium stearate
4 g lactose

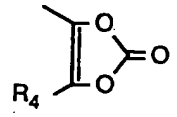
The pulverulent substances are forced through a sieve having a mesh width of 0.6 mm and mixed thoroughly to yield a total of 230 g. 1000 gelatine capsules are each filled with 330 mg of this mixture using a capsule filling machine.

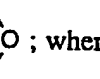
What we claim is:

1. A compound of the formula (I)



(I)

in which R represents -(CO)-R_1, -O-(CO)-R_2, -O-(CO)-O-R_3 or  wherein

R_1 is -NR_4R_5 or  ; whereby R_4 and R_5 are independent of each other C_1-C_3 alkyl or C_3-C_7 cycloalkyl or form together the group -$(CH_2)_n$-, n is an integer from 3 to 6;
R_2 is C_1-C_6 alkyl, unsubstituted phenyl or phenyl substituted by one to four substituents selected from the group consisting of halogen and hydroxy;
R_3 is C_1-C_6 alkyl or C_3-C_7 cycloalkyl;
R_4 is C_1-C_3 alkyl; and salts thereof.

2. A compound of the formula (I) according to claim 1 in which
R_1 is -NR_4R_5 whereby R_4 and R_5 are independent of each other C_1-C_3 alkyl;
R_2 is C_1-C_3 alkyl;
R_3 is C_1-C_3 alkyl or C_3-C_7 cycloalkyl; halogen is fluorine, chlorine or bromine; cycloalkyl is cyclohexyl; and
R_4 is methyl; and salts thereof.

3. A compound of the formula (I) according to claim 1 in which R represents -O-(CO)-R_2 and R_2 is C_1-C_6 alkyl, preferably C_1-C_3 alkyl; and salts thereof.

4. A compound according to claim 1 selected from the group consisting of
Bis N,N'-diethylaminocarbonylmethyl-[N,N-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;

Bis acetoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis n-propoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis iso-propoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N N'-diacetate;
Bis acetoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis tert-butoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis n-pentoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis phenoxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis ethoxycarbonyloxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis cyclohexyloxycarbonyloxymethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate;
Bis (4-methyl-1,3-dioxolan-2-on-4-yl)methoxy-[N,N'-bis(2-hydroxybenzyl)]-ethylenediamine N,N'-diacetate. and
Bis N-morpholinocarbamoylmethyl-[N,N'-bis(2-hydroxybenzyl)]ethylenediamine N,N'-diacetate.

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof according to claim 1.

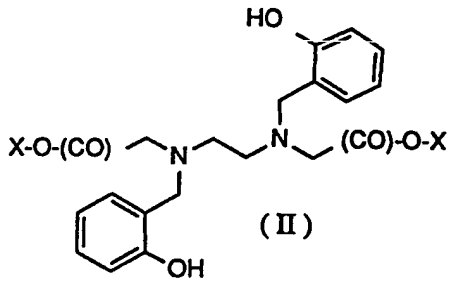
6. A pharmaceutical composition according to claim 5 for systemic, preferably oral administration comprising a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof according to claim 1 together with a carrier suitable for oral uptake.

7. A method of treatment of pathological conditions in a mammal that are associated with an excess of trivalent metal ions in the body, comprising administering systemically to said mammal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1.

8. A method according to claim 7 comprising the oral administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1 together with a carrier suitable for oral uptake.

9. Process for the production of a compound of the formula (I) according to claim 1 comprising adding under cooling sodium hydride or potassium hydrogene carbonat to the

compound of the formula (II)



(II)

wherin X stands for hydrogen or the group $-CH_2J$ and adding to the resultant solution either

(a) in those cases where X stands for hydrogen a compound of the formula (III)

$$Y\text{-}CH_2\text{-}R \text{ (III), or}$$

(b) in those cases where X stands for the group $-CH_2J$ a compound of the formula (IV)

$$HO\text{-}C(O)\text{-}R \text{ (IV),}$$

whereby R in the formulae (III) and (IV) is defined as under formula (I) and Y represents halogen.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/IB 94/00388

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/16 A61K31/22 C07C235/06 C07D295/18 C07D317/40
A61K31/535 A61K31/335

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 528 196 (C.G. PITT) 9 July 1985 cited in the application ---	1-8
A	EP,A,0 403 243 (MERCK FROSST CANADA INC.) 19 December 1990 -----	1-6,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 1995	27. 01. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sánchez García, J.M.

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INTERNATIONAL SEARCH REPORT

information on patent family members

Intern. al Application No
PCT/IB 94/00388

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4528196	09-07-85	NONE		
EP-A-0403243	19-12-90	CA-A-	2019035	16-12-90
		JP-A-	3081295	05-04-91
		US-A-	5248764	28-09-93